Longitudinal Changes in Kidney Function Estimated from Cystatin C and Its Association with Mortality in Elderly Women

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Keywords

Glomerular filtration rate · Cystatin C · Chronic kidney disease · Aging · Mortality

Abstract

Background/Aims: Prospective data on age-related changes in kidney function are required, especially since the current Kidney Disease Improving Global Outcomes (KDIGO) definition has been suggested to classify a large number of elderly people with CKD. **Objective:** This study, a complement to our previous Cr-based study in the same cohort, is aimed at evaluating cystatin C (cysC)-based changes in kidney function during aging in older women and analyzing the association between CKD and mortality through 10 years of follow-up. **Methods:** cysC was available in 981 women from the Osteoporosis Prospective Risk Assessment (OPRA) cohort, all aged 75 years on entry. Reinvestigations were made after 5 ($n = 685$) and 10 years ($n = 365$). Kidney function was estimated (estimated glomerular filtration rate [eGFR]) using Chronic Kidney Disease Epidemiology Collaboration cysC and Caucasian, Asian, Pediatric, and Adult cysC equations and the change in function calculated. Women were staged equivalent to CKD stage 1, 2, 3a, or 3b–5 according to the KDIGO classification. Mortality risk was estimated for 5-year

or 10-year follow-up time using Cox proportional hazard analyses (reference category, CKD stages 1 and 2). **Results:** Mortality risk for women with the worst kidney function (CKD stages 3b–5) increased during both 5-year follow-up times compared to that for women in stages 1 and 2 (age 75–80 years: adjusted Hazard Ratio [HR_{adj}] 3.9, 95% confidence interval [CI] 2.3–6.5; age 80–85 years: HR_{adj} 1.7, 95% CI 1.0–2.7). In contrast, women in stage 3a had increased risk only in the first 5-year follow-up (HR_{adj} 1.7, 95% CI 1.0–3.0, age 75–80 years). Change in kidney function amounted to a loss of $1.9 (\pm 1.4)$ mL/min/1.73 m² per year during the 10-year follow-up, and at age 85 years, 4 of every 5 women had an eGFR equivalent to CKD. **Conclusion:** In the future, an age-adapted definition of CKD, lowering the threshold for CKD in the elderly, may be beneficial to avoid overdiagnosis of CKD.

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Introduction

Today, the world faces an increasingly elderly population and correspondingly increasing demands on health care. Kidney function and its decline are an inevitable part of aging [1, 2], but the clinical implications of this

decline and at which point physiology turns into pathology are being debated. Age-related studies of kidney dysfunction are scarce [3], and those available are heterogeneous regarding study populations and methods to estimate kidney function. Hence, we lack a clear picture of the normal aging process. Therefore, the age-related decline in kidney function and its clinical consequences need thorough investigation in the older population to avoid over- and underdiagnosis.

Kidney function is categorized into stages 1–5 in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. CKD is defined as stages 3–5 (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²), even when kidney morphology and urine albumin-to-Cr ratio are normal [4]. This threshold is based on a mortality risk increase at an eGFR below 60 mL/min/1.73 m², observed primarily among relatively young individuals aged 55–64 years. However, the association between mortality risk and kidney function might in part be age dependent, as demonstrated by the fact that at younger ages, even with an apparently adequate function (eGFR < 75 mL/min/1.73 m², stages 2–5), mortality risk is increased [5–7]. Elderly individuals must have considerably more impaired function to have a similar magnitude of risk (eGFR < 45 mL/min/1.73 m², stages 3b–5) [8–10].

Given this apparent age dependency, there is an ongoing discussion about the clinical implications of age-related decline in kidney function [6, 11–13]. Existing KDIGO definition and therapy recommendations do not take age into consideration – an eGFR < 60 mL/min/1.73 m² equates to CKD, be the patient 25 or 105 years old. While defenders of the current definition claim that early CKD detection might delay critical disease progression, for most individuals, kidney disease develops slowly over decades [4]. Critics of the current definition argue that early age-related decline should be seen as a part of normal aging and not as CKD [14], therefore suggesting lowering the threshold to eGFR < 45 mL/min/1.73 m² (stages 3b–5) in older individuals [7, 15]. We have previously addressed the lack of longitudinal data on kidney function using a cohort of elderly women followed up for 10 years. Using five Cr-based study equations, we demonstrated that by age 85 years, every other woman had an eGFR equivalent to CKD. However, stages 3b–5, and not stage 3a, were associated with increased mortality risk [16].

The present complementary study performed in the same cohort had 2 aims: First, to use cystatin C (cysC) with 2 of the most common study equations to investigate age-related changes in kidney function and estimate the

proportion of women with an eGFR equivalent to CKD. The rationale for using cysC is that this endogenous GFR marker is proposed to be more accurate, particularly in older people [17], and is a stronger marker for cardiovascular events [18]. Second, we sought to investigate the association between kidney function and mortality risk in elderly women and determine the eGFR threshold at which risk is increased in 75-year-olds and at the advanced age of 80 years.

Materials and Methods

Subjects

The population-based Osteoporosis Prospective Risk Assessment (OPRA) cohort, designed as a bone health study, consists of 75-year-old women [19] followed up for 10 years. From 1995 to 1998, 1604 women were invited by letter to participate in the study on their 75th birthday. The women were randomly selected without exclusion criteria; 1,044 women chose to participate in the study (65% response rate). Reinvestigations were made at age 80 and 85 years, with 715 and 383 returning, respectively. Reasons for nonattendance and the number of women who died between visits have been described in detail previously [16]. The present study includes only women for whom cysC-based eGFR values were available; at each visit, this was 981 (age 75 years), 685 (age 80 years), and 365 women (age 85 years). Hence, missing cysC values correspond to 63 (6%), 30 (4%), and 18 (5%) at ages 75, 80, and 85 years, respectively. The study was performed in accordance with the Helsinki Declaration and approved by the local Ethics Committee. Participants provided written informed consent.

General Chemistry and Kidney Function

Between 8:00 a.m. and 1:00 p.m., non-fasting blood samples were collected, centrifuged, and stored at –80°C. Routine blood chemistry was analyzed by standard methods.

Plasma cysC was analyzed in batch at all time points (ages 75, 80, and 85 years) using a particle-enhanced immunoturbidimetric method and adjusted to the international cysC reference preparation ERM-DA 471/IFCC (coefficient of variation 2.2–1.1%), as described in detail previously [20]. Based on cysC, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration cysC (CKD-EPI_{cysC}) formula [21] and the Caucasian, Asian, Pediatric, and Adult cysC (CAPA_{cysC}) cohort study equation [22]. Both formulas (shown below) are adjusted for body surface area and presented in mL/min/1.73 m².

$$\text{CKD-EPI}_{\text{cysC}}$$

$$\text{p-cysC} \leq 0.8: 133 \times (\text{p-cysC}/0.8)^{-0.499} \times 0.996^{\text{Age}} \times 0.932,$$

$$\text{p-cysC} > 0.8: 133 \times (\text{p-cysC}/0.8)^{-1.328} \times 0.996^{\text{Age}} \times 0.932,$$

$$\text{CAPA}_{\text{cysC}}$$

$$130 \times \text{p-cysC}^{-1.069} \times \text{age}^{-0.117} - 7.$$

CKD staging in our study is based on the eGFR alone in accordance with the 2012 KDIGO guidelines, since data on urine albumin are not available from the OPRA cohort: stage 1 (normal kid-

Table 1. Clinical data for the OPRA cohort at baseline and follow-up visits

	Age 75 years (<i>n</i> = 981)		Age 80 years (<i>n</i> = 685)		Age 85 years (<i>n</i> = 365)	
	mean	SD	mean	SD	mean	SD
Age, years	75.2	0.1	80.2	0.2	85.2	0.14
BMI, kg/m ²	26.3	4.2	26.0	4.2	25.4	4.0
Weight, kg	68	12	66	11	64	11
Height, cm	161	6	159	6	158	6
p-cysC,* mg/L	1.06	0.31	1.18	0.34	1.28	0.39
CKD-EPI _{cysC} , mL/min/1.73 m ²	63	18	54	15	47	14
CAPA _{cysC} , mL/min/1.73 m ²	67	18	59	15	52	14
p-calcium, mmol/L	2.40	0.07	2.41	0.13	2.34	0.09
p-phosphate,* mmol/L	1.11	0.23	1.09	0.19	1.13	0.17
s-PTH,* pmol/L	4.20	2.34	4.61	2.72	4.20	3.14
s-25(OH)D, nmol/L	62	19	78	30	79	26
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Treatment for high blood pressure	386	39	279	41	197	54
Cardiovascular diseases	187	19	165	24	109	30
Heart failure		NA	47	7	40	11
Diabetes	68	7	55	8	28	8
Current smoker	136	14	73	11	20	6

* Median with interquartile range. NA, not analyzed; cysC, cystatin C; SD, standard deviation; CKD-EPI_{cysC}, Chronic Kidney Disease Epidemiology Collaboration cystatin C; CAPA_{cysC}, Caucasian, Asian, Pediatric, and Adult cystatin C; s-25(OH)D, serum Calcifediol; s-PTH, serum parathyroid hormone.

ney function, GFR ≥ 90 mL/min/1.73 m²), stage 2 (mild reduction, GFR 60–89), stage 3a (mild to moderate reduction, GFR 45–59), stage 3b (moderate to severe reduction, GFR 30–44), stage 4 (severe reduction, GFR 15–29), and stage 5 (established kidney failure, GFR < 15). CKD is defined as stage 3 or higher [4].

Mortality

Mortality was followed up for the entire study duration (10 years) and the date of death recorded through the Swedish National Population Register [23]. Information on the cause of death was not available.

Other Variables

Height (cm) and weight (kg) were measured by standardized methods at each follow-up and BMI calculated (kg/m²). Information about comorbidities (diabetes, cardiovascular diseases, treatment for high blood pressure, and heart failure) is self-reported and collected from questionnaires at all visits, as described previously [16].

Statistics

Descriptive data are presented as mean with SD or median with interquartile range, as appropriate. Differences in the mean eGFR between the CKD-EPI_{cysC} and CAPA_{cysC} formulas were estimated using the paired sample *t* test.

Change in kidney function was calculated individually for every woman as actual eGFR change per 5 or 10 years (mL/min/1.73 m²) or as annual percentage change (%), between the time intervals, ages 75–80 years (*n* = 650), 80–85 years (*n* = 336), and 75–85 years (*n* = 346), as described in Ref. [16]. We also investigated

change in kidney function over time using a mixed model with a random intercept. In this model, kidney function (eGFR estimated by CKD-EPI_{cysC}) was used as a linear variable using all 3 time points (ages 75, 80, and 85 years). Differences in mean estimates of the baseline GFR between women who gained versus lost kidney function during the follow-up were compared using the independent sample *t*-test. As an additional sensitivity analysis, we also looked at change in the eGFR between the first and second 5 years using only women who attended the entire follow-up (*n* = 346).

Proportion of women with an eGFR equivalent to CKD was calculated for each visit (ages 75, 80, and 85 years). We also investigated stability of this low eGFR over time, that is, how many women with an eGFR equivalent to CKD stages 3–5 at age 75 years remained in these stages at 80 years and, similarly, resetting baseline at age 80 years and assessing stability of the eGFR equivalent to CKD at age 85 years. These longitudinal calculations are based on women who attended 2 consecutive visits and had available cysC values (*n* = 650 women had consecutive cysC values at ages 75 and 80 years; *n* = 336 at ages 80 and 85 years). For completeness, we also performed an additional sensitivity analysis using only women who attended the entire follow-up.

For mortality risk calculations, women were categorized by CKD stage into three groups: (i) normal to mild reduction of kidney function, eGFR > 60 mL/min/1.73 m² (stages 1 and 2); (ii) mild to moderate reduction, eGFR 45–59 mL/min/1.73 m² (stage 3a); and (iii) moderate to severe reduction, eGFR < 45 mL/min/1.73 m² (stages 3b–5), and Cox proportional hazard analyses were performed. Log-log plots were used to confirm the proportional hazard assumptions. The association with mortality was also investigated using the eGFR as a continuous variable.

Fig. 1. Prevalence and development of CKD using the CKD-EPI_{cysC} and CAPA_{cysC} formulas based on cysC. At 10 years (age 85 years), proportionally more women (13%) were at CKD stages 3–5 by CKD-EPI_{cysC} versus CAPA_{cysC}. cysC, cystatin C; CKD-EPI_{cysC}, Chronic Kidney Disease Epidemiology Collaboration cystatin C; CAPA_{cysC}, Caucasian, Asian, Pediatric, and Adult cystatin C.

Analyses are presented as both unadjusted and adjusted for diabetes, cardiovascular diseases, smoking habits, and treatment for high blood pressure (age 75 years), with additional adjustment for heart failure, at age 80 years. Follow-up times for mortality risk calculations are 5 and 10 years, that is, from ages 75–80 and 75–85 years. To investigate this association in advanced age, we “reset” baseline at age 80 years and calculated 5-year mortality risk between 80 and 85 years. As a sensitivity analysis, the baseline eGFR for women who continued in the study was compared to that of those who died or dropped out using the independent sample *t* test.

The data presented are secondary, exploratory analyses; hence, power calculations are not stated. A priori power analyses prior to collection of the cohort have been reported previously [20].

Analyses were performed with SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, USA: IBM Corp.). A *p* value <0.05 was considered nominally significant.

Results

The eGFR and characteristics of the studied population are reported in Table 1. The CKD-EPI_{cysC} study equation estimated a lower mean eGFR than the CAPA_{cysC} equation at all ages (*p* for all <0.001).

Proportion of Women with eGFR Equivalent to CKD

Since the present age-independent definition of CKD may misclassify a large number of elderly people with disease, we evaluated the proportion of women with an eGFR equivalent to CKD stages 3–5 in the OPRA cohort at different ages (75, 80, and 85 years). In cross-sectional analyses, regardless of the study equation used, the proportion with an eGFR corresponding to CKD doubled by the end

Table 2. Risk of mortality for women with CKD (stages 3a and 3b–5) compared to women with normal kidney function (stages 1 and 2)

	Stages 1 and 2	CKD-EPI _{cysC}				CAPA _{cysC}			
		stage 3a		stages 3b–5		stage 3a		stages 3b–5	
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<i>Estimated 5-yr risk (age 75–80 years)</i>	(n*)	(n = 252)		(n = 159)		(n = 234)		(n = 110)	
Unadjusted	1 (ref)	1.8 (1.1–3.1)	0.029	4.2 (2.5–6.9)	<0.001	1.9 (1.1–3.2)	0.015	4.9 (3.0–8.2)	<0.001
Model 1	1 (ref)	1.7 (1.0–3.0)	0.049	3.9 (2.3–6.5)	<0.001	1.8 (1.1–3.0)	0.030	4.6 (2.8–7.8)	<0.001
<i>Estimated 10-yr risk (age 75–85 years)</i>		(n = 252)		(n = 159)		(n = 234)		(n = 110)	
Unadjusted	1 (ref)	1.3 (1.0–1.8)	0.048	2.3 (1.8–3.1)	<0.001	1.6 (1.2–2.1)	0.001	2.8 (2.1–3.8)	<0.001
Model 1	1 (ref)	1.3 (0.9–1.7)	0.122	2.3 (1.7–3.1)	<0.001	1.5 (1.1–2.0)	0.004	2.7 (2.0–3.8)	<0.001
<i>Estimated 5-yr risk (age 80–85 years)</i>		(n = 265)		(n = 184)		(n = 262)		(n = 107)	
Unadjusted	1 (ref)	1.1 (0.7–1.8)	0.627	1.9 (1.2–3.0)	0.008	1.3 (0.8–2.0)	0.279	2.7 (1.7–4.4)	<0.001
Model 1**	1 (ref)	1.1 (0.7–1.8)	0.716	1.7 (1.0–2.7)	0.045	1.3 (0.8–2.0)	0.296	2.5 (1.5–4.2)	<0.001

CI, confidence interval; CKD-EPI_{cysC}, Chronic Kidney Disease Epidemiology Collaboration cystatin C; CAPA_{cysC}, Caucasian, Asian, Pediatric, and Adult cystatin C. Risk estimated using the Cox regression analysis (reference category CKD stages 1 and 2). Model 1: adjusted for diabetes, cardiovascular diseases, smoking habits, and treatment for high blood pressure at age 75 years. Missing values at age 75 years: smoking habits (*n* = 11). Missing values at age 80 years: diabetes (*n* = 1), cardiovascular diseases (*n* = 1), smoking habits (*n* = 7), treatment for high blood pressure (*n* = 1), and heart failure (*n* = 1). * Number in stages 1 and 2 differs depending on the formula used (age 75 years: CKD-EPI_{cysC} *n* = 570, CAPA_{cysC} *n* = 637; age 80 years: CKD-EPI_{cysC} *n* = 236, CAPA_{cysC} *n* = 316). ** Adjusted for diabetes, cardiovascular diseases, smoking, treatment for high blood pressure, and heart failure at age 80 years.

of the study period (Fig. 1). At all ages, CKD-EPI_{cysC} classified proportionally more women as having CKD stages 3–5 than CAPA_{cysC}, meaning that by the 10-year follow-up, 84% of these otherwise healthy women had CKD stages 3–5 compared to 71% by CAPA_{cysC}, a 13% difference (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000507256). Point-prevalence calculations based only on women attending the entire follow-up were very slightly lower.

According to the KDIGO guidelines, 2 consecutive eGFR measurements are needed for a correct CKD diagnosis. In the OPRA cohort, longitudinally, the vast majority (92%) of women with CKD stages 3–5 at age 75 years remained within these stages at age 80 years. From age 80 years and forward, almost all (97%) women with CKD stages 3–5 remained in these stages at 85 years.

Loss to follow-up is inevitable in an elderly cohort across 10 years; with the aim of validating our results, we investigated whether kidney function in women who continued to participate in the study differed from women who did not participate (through choice or death). Both at baseline and follow-up assessments, the eGFR differed with participation status. Among women who attended the first follow-up at 5 years/80 years, the baseline eGFR was higher than that of nonparticipants (65 ± 17 vs. 59 ± 20 , $p < 0.001$). Similarly, participants at the second follow-up at 10 years/85 years had a higher eGFR at age 80 years than nonparticipants (56 ± 14 vs. 53 ± 15 , $p = 0.002$).

Change in Kidney Function

To calculate the change in kidney function during aging, 5- or 10-year time intervals were investigated, that is, from baseline (75–80 years and 75–85 years) and from the first follow-up (80–85 years). Across 10 years, change in kidney function equated to an actual loss in the eGFR (CKD-EPI_{cysC}) of 19 ± 14 mL/min/1.73 m² overall, higher during the first 5 years (11 ± 12 ; 75–80 years) and somewhat lower in the latter 5 years (9 ± 10 ; 80–85 years). This was equivalent to a 2.6% (± 2.1) loss per year during the entire follow-up, stable across both 5-year intervals (3% [± 4] and 3% [± 3]). The mixed-model analysis estimated that the yearly change in the eGFR would be a loss of 1.83 (95% CI 1.71–1.95) mL/min/1.73 m², which closely mirrors the actual loss over 10 years. Estimates by CAPA_{cysC} were essentially similar (10-year change: loss per year $22 [\pm 14]$ mL/min/1.73 m²; 2.3% [± 2.0]). The results from sensitivity analyses in women who attended the entire follow-up were almost identical (10 ± 12 mL/min/1.73 m² in the first 5 years; 9 ± 10 mL/min/1.73 m² in the latter 5 years). Likewise, percentage loss per year was identical.

Although mean kidney function in the entire cohort declined, kidney function improved in 38 women (11%), with a mean gain of 2% (± 1) per year between ages 75 and 85 years. At baseline, these women had a considerably lower eGFR than women whose kidney function subsequently declined ($46 [\pm 12]$ vs. $69 [\pm 15]$, $p < 0.001$).

Fig. 2. Kidney function at age 75 years based on CKD-EPI_{cysC} or CAPA_{cysC} and 10-year survival. CKD-EPI_{cysC}, Chronic Kidney Disease Epidemiology Collaboration cystatin C; CAPA_{cysC}, Caucasian, Asian, Pediatric, and Adult cystatin C. Data is unadjusted. *p* values represent *p* for difference, calculated using the log rank test. CKD-EPI_{cysC} stage 1–2 (*n* = 570), stage 3a (*n* = 252), stage 3b–5 (*n* = 159). CAPA_{cysC} stage 1–2 (*n* = 637), stage 3a (*n* = 234), stage 3b–5 (*n* = 110).

Kidney Function and Mortality

Due to the current debate about a potential age-dependent CKD definition, we wanted to explore the relationship between age-related decline in kidney function and mortality. The CKD-EPI_{cysC} study equation estimated a two-fold mortality risk increase in women with the worst baseline kidney function (stages 3b–5) compared to those with normal function (HR_{adj} 2.3, 95% CI 1.7–3.1, Table 2; Fig. 2) in the long follow-up (i.e., the 10 years between ages 75 and 85 years). The risk increase was apparent in each of the 5-year intervals (ages 75–80 and 80–85 years). In contrast, women with mild to moderate reduction (stage 3a) had a risk increase only in the initial interval, that is, the 5 years between ages 75 and 80 years (HR_{adj} 1.7, 95% CI 1.0–3.0). Over 10 years (75–85 years) or in advanced age (80–85 years), the risk was slightly but non-significantly increased. Using the CAPA_{cysC} study equation, results for women in stages 3b–5 were generally the same, while women in stage 3a had an increased risk of death for up to 10 years (HR_{adj} 1.5, 95% CI 1.1–2.0). Using the eGFR as a continuous variable, mortality risk decreased per unit increase in the eGFR, a significant association, independent of the study equation and follow-up time (data not shown).

Discussion

This longitudinal cysC-based study, designed as a complement to our previous Cr-based study in the same cohort [16], investigates kidney function during 10 years of aging in older, identically aged women. We show that using cysC, the proportion of women with an eGFR equivalent to CKD stages 3–5 is high at these ages, regardless of the study equation used. Indeed, compared to the Cr-based estimates published previously for these women [16], cysC-based estimates classify a considerably larger proportion in stages 3–5. We also demonstrate that women with the worst kidney function (stages 3b–5) have a two-fold increase in mortality risk, while it is less clear among women with a mild to moderate reduction (stage 3a). We have mapped kidney function and its change over time in elderly women. Through 2 separate studies, we have comprehensively assessed how the markers, Cr and cysC, influence GFR estimates and how the different study equations affect estimates.

Since kidney function naturally declines with aging, often below the threshold of CKD diagnosis, the present KDIGO definition may unnecessarily classify a large number of elderly people with CKD. In elderly women,

by age 85 years, the mean kidney function had dropped by 16 points to 47 mL/min/1.73 m² using CKD-EPI_{cysC}, well below the threshold for CKD. In other words, 8 of 10 women (84%) had an eGFR equivalent to CKD, even though the vast majority were only in stage 3a, and probably unlikely to progress into kidney failure. Whether the women in the OPRA cohort truly have CKD by the present definition cannot be correctly diagnosed by a single measurement, since low kidney function (or albumin-to-Cr ratio) should persist over time for a correct diagnosis [3, 4]. In line with this, our longitudinal data showed improved function in a proportion of women. While lacking detailed medical histories, we can only speculate on whether a concurrent illness such as acute kidney injury or hemodynamic change caused a transient increase in the eGFR. However, the cross-sectional point prevalence of CKD_{cysC} appears to be higher in the OPRA cohort than other studies, possibly due to the heterogeneity of other populations, especially regarding age span, analytical methods, and study equations [16, 24–26]. Environmental and lifestyle factors may also affect CKD prevalence between countries [27].

The very high proportion of the eGFR corresponding to CKD in otherwise healthy elderly women leads us to support the proposition of an age-adapted CKD definition [6–8, 28, 29]. Another reason for advocating this is that in advanced age, mortality risk was not increased in women with only a mild to moderate reduction (stage 3a), regardless of the cysC study equation used. In contrast, at age 75 years, women with an eGFR corresponding to CKD stage 3a were at increased risk.

A specific age-adjusted definition, with a lowering of the threshold to 45 mL/min/1.73 m² in patients aged 65 years and older, has been suggested [13]. Our observations support that at least in the oldest old, an age-adapted CKD classification could be of value to avoid overdiagnosis of CKD and, in addition, avoid unnecessary psychological cost to the patient.

This study has several strengths. First, kidney function estimates are based on cysC, which is proposed to be more appropriate in the elderly; despite this, Cr is commonly used in most studies. A key strength is that in this all female, identically aged cohort, the cysC estimates of eGFR can be directly compared with Cr estimates available in the same women. Taken together, this provides essential evidence regarding the clinical implications of marker choice and study equation, since we show the point prevalence of CKD in 75-year-old women ranges from 15 to 33% using Cr-based equations and 35–42% using cysC-based equations. Another strength is the long

follow-up, enabling comparison of kidney function over time and allowing mortality risk to be estimated over different time intervals. A major cause of potential confounding is eliminated by the study design whereby all participants are the same age and sex. It is acknowledged, however, that while adjustment for covariates was performed, unmeasured confounders cannot be ruled out and the results should be interpreted with this in mind. Last, the high participation rate and large sample size are 2 important strengths.

Limitations are acknowledged; the measured GFR was not a part of the study protocol. However, eGFR is an everyday tool for the clinician and commonly used in population studies. In selecting the study equations, we chose CKD-EPI_{cysC} because it is the most widely used internationally, even though few elderly subjects were included in its development [21]. To counterbalance this, we also chose CAPA_{cysC} [22], which did include elderly subjects in its development. Likely, it performs better than CKD-EPI_{cysC} in this age-group [24, 25]. Furthermore, another equation using cysC is Full Age Spectrum equation (FAS), showing comparable performance as CAPA [30]. Availability of urinary albumin measurements is a prerequisite to define stages 1 and 2 but not necessary for defining stage 3 and higher. Urinary albumin is also a strong risk factor for progression of CKD. Lack of urinary albumin is a limitation of this study, and as CKD was based only on GFR levels, we cannot differentiate between lower stages of CKD. Nevertheless, the use of eGFR estimations from 3 different time points enables comparisons over time and therefore evaluation of chronicity of kidney function. We acknowledge that the study participants may be healthier than the general population and that the observed diminution in the magnitude of decline in kidney function at advanced age may be attributable to survival bias (since those who continued to participate in the study had a higher baseline eGFR) [31]. However, this also emphasizes that kidney function below the threshold of CKD is high even among generally healthy elderly women. We also acknowledge that the 10-year analyses are based on a reduced number of women. However, loss to follow-up through death and diseases is unavoidable in studies of these ages and long duration. Last, all participants are Caucasian, resident in one city, and with assumed similar environmental exposures; therefore, results might not be generalizable to males, other ethnicities, or countries.

This cysC-based study was planned as a complement to our previous Cr-based one with the aim of getting a step closer to accurately understanding and describing

age-related changes in kidney function. Our findings based on cysC show that the proportion of women classified with CKD doubles from age 75 to 85 years and amounts to 4 in 5 at age 85 years. While cysC-based estimations of CKD stages 3b–5 are associated with mortality even in advanced age, an increased risk for women in stage 3a is seen only in the first 5-year follow-up time. An age-adapted definition of CKD in the future, lowering the threshold for CKD in the elderly people, may be beneficial to avoid overdiagnosis of CKD.

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Statement of Ethics

Participants in the OPRA study have given written informed consent, and the study protocol has been approved by the Regional Ethical Review Board in Lund. The study was conducted in accordance with the Helsinki Declaration.

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Author Contributions

L.M., F.M., A.C., and K.Å. contributed to the conception or design, or analysis and interpretation of data, or both. L.M. takes responsibility for the integrity of the data analysis. L.M., M.F., and K.Å. helped drafting the manuscript and L.M., F.M., A.C., and K.Å. revised the manuscript. L.M., F.M., A.C., and K.Å. provided intellectual content of critical importance to the work. L.M., F.M., A.C., and K.Å. contributed to the final approval of the version to be published. L.M., F.M., A.C., and K.Å. agreed to be accountable for accuracy and integrity of the work.

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